IJPSR (2012), Vol. 3, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 June, 2012; received in revised form 22 September, 2012; accepted 28 September, 2012

COMPARISON OF VARIOUS NATURAL SUPERDISINTEGRANTS IN THE FORMULATION OF FAST DISSOLVING CARVEDILOL TABLET

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Keywords:
Superdisintegrant, Carvedilol, Fenugreek, *Lepidium sativum*, *Plantago ovata*, Guar gum, Fast dissolving tablet

Abbreviations:
FDT - Fast dissolving tablet
MDT - Mouth dissolving tablet
MCC - Micro crystalline cellulose
DT - Disintegration time

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ABSTRACT

In the present investigation, fast dissolving tablets of Carvedilol were formulated by using various natural superdisintegrant like *Plantago ovata*, *Lepidium sativum*, Fenugreek and Guar gum. A Direct compression method was used to prepare fast dissolving tablets containing Carvedilol as a model drug using natural superdisintegrants. Prepared formulations were evaluated for Precompression parameters such as micromeritic properties like angle of repose, %compressibility and Hausner's ratio. Tablets were also subjected to Postcompression analysis for the parameters such as weight variation, hardness, and friability, *in vitro* disintegration time, wetting time, drug content and *in vitro* dissolution study. The results concluded that amongst all formulations, the formulation prepared with mucilage of *Plantago ovata* showed better disintegrating property as well as the release profile than the other used natural superdisintegrant.

INTRODUCTION: Natural gums and mucilages are preferred over semi-synthetic and synthetic excipients in the field of drug delivery because they are cheap and easily available, have soothing action and non-irritant nature. Further, they are eco-friendly, capable of multitude of chemical modifications, potentially degradable and compatible due to their natural origin [1-2]. Polymers have been successfully investigated and employed in the formulation of solid, liquid and semi solid dosage forms and are specifically useful in design of novel drug delivery system. Both synthetic and natural polymer have been investigated extensively for this purpose [3]. Synthetic polymers are toxic, expensive, have environmental related issues, need long development time for synthesis and are freely available in comparison to naturally available polymers. However the use of natural polymer for pharmaceutical application is attractive because they are economical readily available, non-toxic and capability of chemical modification, potentially biodegradable and few exceptions also biocompatible.

A large number of plant based pharmaceutical excipient is available today. Many researchers have explored the usefulness of plant based materials as pharmaceutical excipients. Availability to produce a wide range of material based on their properties and molecular weight [4].

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Natural polymers have become a thrust area in majority of investigation in drug delivery system. Natural gums have also been modified to meet the requirements of drug delivery system and thus can compete with synthetic excipient available in the market [5].

Natural Superdisintegrants: Today, we have a number of plant-based pharmaceutical excipients and various researchers have explored the utility of some of these plant-based materials as Pharmaceutical Super-disintegrant. Plant products serve as an alternative to synthetic products because of local accessibility, eco-friendly nature, bio-acceptable, renewable source and lower prices compared to important synthetic products. Majority of investigations on natural polymers for disintegrant activity are centered on polysaccharides and proteins, due to their ability to produce a wide range of materials and properties based on their molecular structures [6].

Description of Natural Superdisintegrants:

***Lepidium Sativum*:** *Lepidium sativum* (family: Cruciferae) is known as asaliyo and is widely used as herbal medicine in India. It is widely available in market and has very low cost. Parts used are leaves, root, oil, seeds etc as shown in **fig. 1**. Seeds contain higher amount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E and F and two new monomeric imidazole alkaloids semilepidinoside A and B. Mucilage of *Lepidium sativum* has various characteristic like binding, disintegrating, gelling etc. respectively [7].

A

B

FIG. 1: IMAGES OF *LEPIDIUM SATIVUM* (A) LEPIDIUM SEED (B) LEPIDIUM HERB

Plantago Ovata: Isapghula Husk consists of dried seeds of the plant known as plantago ovata as shown in **fig. 2**. The plant contains mucilage in the epidermis of the seeds. Mucilage of *Plantago ovata* has various characteristics like binding, disintegrating and sustaining properties. Mucilage can be used as superdisintegrant to formulate fast dissolving tablets because it has very high percentage of swelling index (around 89±2.2%v/v) as compared to the other super disintegrating property [8].

A

B

FIG. 2: *PLANTAGO OVATA* – A) SEED, B) HUSK

Fenugreek: *Trigonella foenum-graceum* (family Leguminosae), commonly known as Fenugreek, is an herbaceous plant of the leguminous family. It is one of the oldest cultivated plants and has found wide applications as a food, a food additive, and as a traditional medicine in every region. Fenugreek seeds as shown in **fig. 3**, contain a high percentage of mucilage which can be used as disintegrant for use in mouth dissolving tablet formulations. Mucilage is an off white-cream yellow colored amorphous powder that quickly dissolves in warm water to form viscous colloidal solution [8].

FIG. 3: FENUGREEK SEEDS

Guar Gum: Guar gum comes from the endosperm of the seed of the legume plant *Cyamopsis tetragonolobus.* Guar gum is prepared by first drying the pods in sunlight, then manually separating from the seeds. The gum is commercially extracted from the seeds as shown in **fig. 4,** essentially by a mechanical process of roasting, differential attrition, sieving and polishing. Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches [9].

FIG. 4: GUAR GUM SEEDS

Carvedilol (BCS Class II drug) is a nonselective β-adrenergic blocking agent with α1-blocking activity and it is mainly used in the management of hypertension. Hence, in the present research work FDTs of Carvedilol were prepared by direct compression technique using different concentrations of natural superdisintegrant like *Plantago ovata, Lepidium sativum*, Fenugreek and Guar gum to study and compare their release rate of prepared formulaion.

MATERIALS AND METHODS: Seeds of *Lepidium sativum*, Fenugreek and *Plantago ovata* were purchased from the local market Khari bawli of Chandni Chowk, New Delhi and Carvedilol was obtained as a gratis sample from Ranbaxy Pvt. Ltd., India. Other materials including Guar gum powder and excipients used in study were of pharmaceutical grade.

Preparation of seed powder of *Plantago ovata*: The dried *Plantago ovata* seeds were comminuted and sieved through mesh# 80 and stored in desiccator.

Preparation of Lepidium sativum seed powder: The seeds of *Lepidium sativum* (100g) containing the mucilage were boiled with distilled water (1 litre) for 15 minute and the mass was filtered through Buckner funnel without filter paper. The retained residues were boiled with distilled water (0.5 litre) for 15 minute and the combined liquid was passed through eight folds of muslin cloth. The mucilage was precipitated from the filtrate by adding ethanol. The precipitated mucilage was dried in an oven at 45^{o}C till it was completely dried. The powder was passed through 80 # mesh sieve and weighed to calculate the yield.

Preparation of Fenugreek seeds powder: The dried fenugreek seeds were collected and size reduction was done in the grinder then sieved through mesh # 80 and stored in desiccator.

Preparation of Fast Dissolving Tablets: Fast dissolving tablets containing 200 mg of Carvedilol were prepared by direct compression method, each tablet containing 50 mg of Carvedilol was prepared by using Direct compression as per Formula given in **Table 1 and 2**. The superdisintegrant *Plantago ovata* (5%, 10%, 15%), Fenugreek (5%, 10%, 15%), *Lepidium sativum* (5%, 10%, 15%) and Guar Gum (5%, 10%, 15%) were used in different proportion and in different combination. All the ingredients were passed through sieve # 60 and

kept in hot air oven at 60^{o}C to make anhydrous and accurately weighed. The drug, superdisintegrant, MCC, Mannitol were mixed to improve drug distribution and content uniformity and triturated well in a mortar. Then Mag. Stearate and Talc was passed through sieve # 80, mixed and blended well with the initial mixture. The mixed blend of Drug and Excipient was compressed using single Punching Machine to produce tablet weighing 200 mg having diameter 4.5mm, following the procedure twelve batches of MDT of Carvedilol in different ratio of superdisintegrant were prepared.

TABLE 1: FORMULATIONS OF CARVEDILOL CONTAINING DIFFERENT CONCENTRATIONS OF DIFFERENT SUPERDISINTEGRANT

Formulation	Carvedilol (mg)	*Plantago ovata* (mg)	*Lepidium sativum* (mg)	MCC (mg)	Mannitol (mg)	Talc (mg)	Mag. stearate (mg)	Total wt. (mg)
AP1	50	10	_	125	5	6	4	200
AP2	50	20	_	115	5	6	4	200
AP3	50	30	_	105	5	6	4	200
AL4	50	_	10	125	5	6	4	200
AL5	50	_	20	115	5	6	4	200
AL6	50	_	30	105	5	6	4	200

***AP1 to *AP3=** Formulation containing Plantago ovata as superdisintegrant. (5%, 10%, 15%).

***AL4 to AL6=** Formulation containing Lepidiumsativum as superdisintegrant. (5%, 10%, 15%).

TABLE 2: FORMULATIONS OF CARVEDILOL CONTAINING DIFFERENT CONCENTRATIONS OF DIFFERENT SUPERDISINTEGRANT

Formulation	Carvedilol (mg)	Fenugreek (mg)	Guargum (mg)	MCC (mg)	Mannitol (mg)	Talc (mg)	Mag. stearate (mg)	Total wt. (mg)
AF7	50	10	_	125	5	6	4	200
AF8	50	20	_	115	5	6	4	200
AF9	50	30	_	105	5	6	4	200
AG10	50	_	10	125	5	6	4	200
AG11	50	_	20	115	5	6	4	200
AG12	50	_	30	105	5	6	4	200

***AF7 to *AF9**= Formulation containing Fenugreek as superdisintegrant. (5%, 10%, 15%).

***AG10 to *AG12=** Formulation containing Guar gum as superdisintegrant. (5%, 10%, 15%).

Evaluation of FDTs [10, 11, 12]: The prepared formulations were evaluated for pre-compression parameters like angle of repose, Hausner's ratio and compressibility index by Carr's method. The post-compression parameters such as weight variation, hardness, friability, *in vitro* disintegration time, wetting time, *in vitro* dissolution test, stability studies, also have been studied. All the results were taken in triplicates (±3SD). The weight of the FDT being made was measured to ensure that a FDT contains the proper amount of drug.

The USP weight variation test was run by weighing 20 FDTs individually using electronic digital balance, calculating the average weight and comparing the individual FDT weights to the average. The FDTs meet the USP test if no more than 2 FDTs are outside the percentage limit and if no FDT differs by more than 2 times the percentage limit. The weight variation tolerances for FDTs differ depending on average FDT weight. The Monsanto hardness tester was used for the determination of the hardness of FDT.

FDT was placed in contact between the plungers, and the handle was pressed, the force needed to fracture the FDT was recorded.

The friability of FDTs was determined using Roche friabilator. It included the determination of loss in weight of FDTs by placing pre-weighed FDTs in the apparatus and it was allowed to run for 100 revolutions with the speed of 25 rpm and weighed once again. The difference in the two weights represents friability. The weight loss should not be more than one percent. Six FDTs were tested from each formulation.

In the disintegration time study, FDT was placed into 900 ml distilled water at 37 ± 2°C in the disintegration test apparatus. The disintegration time was defined as the time required for the FDT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen.

A stopwatch was used to measure the disintegration time to the nearest second. Only one FDT was analyzed at a time in order to ensure maximum accuracy.

In wetting time study, the FDT was placed in a petridish of 5.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

In vitro dissolution study (2) was carried out in the USP paddle method (Electrolab TDT - 08 L Dissolution tester USP). 900 ml of the dissolution medium (1%w/v SLS solution in water) was taken in covered vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was set at 100±2 rpm. Sampling was done every one min interval. For each aliquots of 5 ml from the dissolution medium was withdrawn and the same amount of dissolution medium at 37°C was replenished to the dissolution medium. The samples were analyzed in the UV spectrophotometer at 277.5 nm.

TABLE 3: RESULTS OF PRECOMPRESSION PARAMETERS

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of Repose (Θ)	Carr's Index (%)	Hausner Ratio
AP1	0.521	0.68	22°.24′	21.10	1.32
AP2	0.534	0.69	21°.55′	20.34	1.35
AP3	0.541	0.72	22°.30′	22.69	1.36
AL4	0.604	0.75	27°.24′	19.34	1.40
AL5	0.618	0.78	28°.21′	19.21	1.38
AL6	0.621	0.79	28°.31′	20.12	1.30
AF7	0.634	0.74	23°.24′	20.10	1.34
AF8	0.534	0.65	21°.55′	21.34	1.25
AF9	0.548	0.62	24°.30′	22.61	1.31
AG10	0.569	0.71	27°.24′	19.14	1.01
AG11	0.602	0.76	26°.21′	19.65	1.12
AG12	0.565	0.64	28°.31′	19.62	1.21

TABLE 4: DATA FOR POST COMPRESSION ANALYSIS

Formulation	Weight (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability	Disintegration time (s)	Wetting Time (s)	Water Absorption Ratio (%)
AP1	201±2.4	4.67±0.24	4.1±0.018	0.636	28	40	92±0.31
AP2	200±2.3	4.65±0.26	4.2±0.22	0.593	25	38	92±0.11
AP3	199±1.4	4.61±0.24	4.0±0.22	0.491	22	34	93±0.41
AL4	198±1.4	4.63±0.24	4.2±0.22	0.394	44	44	90±0.14
AL5	201±2.4	4.62±0.24	4.3±0.024	0.491	43	46	90±0.18
AL6	202±2.4	4.57±0.24	4.1±0.019	0.392	40	43	91±0.11
AF7	200±2.4	4.58±0.24	4.3±0.018	0.331	45	45±8	85±0.20
AF8	202±2.3	4.60±0.26	4.2±0.22	0.351	42±2	43±1	88±0.51
AF9	199±1.4	4.61±0.24	4.1±0.22	0.384	40±8	42±5	89±0.81
AG10	198±1.4	4.55±0.24	4.0±0.22	0.596	70	86±5	50±0.31
AG11	201±2.4	4.52±0.24	4.3±0.024	0.598	65	80±4	55±0.25
AG12	200±2.4	4.50±0.24	4.1±0.019	0.599	60	70±8	58±0.12

RESULT AND DISCUSSION: The values of pre-compression parameters (**Table 3**) evaluated were found within prescribed limits and indicated good free flowing property. The data obtained from post-compression parameters such as weight variation, hardness, friability, wetting time and *in vitro* disintegration time for FDTs were shown in **Table 4.** In all the formulations, hardness test indicated good mechanical strength, as the hardness of the FDTs was found in the range of 4.50 to 4.67 kg/cm^2. Friability was observed less than 1%, indicated that FDTs had a good mechanical resistance. The FDTs were subjected for evaluation of *in vitro* disintegration time. The *in vitro* disintegration time for all the formulations varies from 22 to 70 sec. It was observed that when *plantago ovata* was used as superdisintegrant (**API to AP3**), the

FDTs disintegrates rapidly within short time. Due to easy swelling ability of mucilage of *plantago ovata* containing FDTs disintegrates rapidly as compared to other FDTs prepared using Lepidium, Fenugreek and Guar gum. It was observed that the *in vitro* disintegration time of the FDTs decreased with increase in the level of mucilage of *plantago ovata*.

In wetting time study, the wetting time was rapid in FDTs of *Plantago ovata* followed by *Lepidium*, Fenugreek and Guar gum. Results were shown in Table 4. This rapid disintegration of the FDTs was due to the penetration of saliva into the pores of the tablet, which lead to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet.

Plantago ovata was effective at concentration, i.e. 15 %. In vitro dissolution study shown in **Table 9** and **Fig. 9** revealed that (**AP3**) is an optimized formulation that releases more than 90% of drug within 60min As compared to the formulation of AG12, AF9 & AL6 shown in **tables 5, 6 and 7 and Fig. 5, 6 and 7**, moreover followed by *Plantago ovata,* Lepidium than Fenugreek and last in the series is Guar gum with minimum drug release within 60 min as shown in Fig. 9.

TABLE 5: *IN-VITRO* DISSOLUTION STUDY OF TRIALS CONTAINING GUAR GUM

Formulation	Percent Drug Release						
	5 (min)	10 (min)	15 (min)	20 (min)	30 (min)	45 (min)	60 (min)
AG10	16.21	24.21	32.46	42.21	46.36	50.24	56.46
AG11	17.46	25.46	34.21	43.42	47.21	53.46	58.21
AG12	18.21	27.21	36.46	45.64	49.06	55.56	62.26

TABLE 6*: IN-VITRO* DISSOLUTION STUDY OF TRIAL CONTAINING FENUGREEK

Formulation	Percent Drug Release						
	5 (min)	10(min)	15 (min)	20 (min)	30 (min)	45 (min)	60 (min)
AF7	22.64	34.06	43.26	50.64	70.54	80.66	88.64
AF8	25.54	36.21	46.20	53.62	72.46	85.43	90.62
AF9	26.21	39.98	50.16	59.11	79.42	87.42	94.21

TABLE 7*: IN-VITRO* DISSOLUTION STUDY OF TRIALS CONTAINING *LEPIDIUM SATIVUM*

Formulation	Percent Drug Release						
	5 (min)	10 (min)	15 (min)	20 (min)	30 (min)	45 (min)	60 (min)
AL4	23.26	34.98	43.56	52.84	71.28	81.26	89.26
AL5	25.87	37.24	47.01	54.06	73.58	85.64	91.26
AL6	26.98	40.64	51.26	59.56	80.42	88.21	94.89

TABLE 8: *IN-VITRO* DISSOLUTION STUDY OF BATCHES CONTAINING *PLANTAGO OVATA*

Formulation	Percent Drug Release						
	5 (min)	10 (min)	15 (min)	20 (min)	30 (min)	45 (min)	60 (min)
AP1	25.19	37.26	46.91	55.98	74.26	85.26	91.24
AP2	26.27	39.21	49.16	58.21	76.25	88.94	95.64
AP3	27.99	42.25	54.24	60.26	83.62	90.26	97.21

TABLE 9. COMPARATIVE DISSOLUTION AMONG OPTIMIZED BATCHES OF AP3, AL6, AF9 & AG12

Formulation	% Drug Release						
	5 (min)	10 (min)	15 (min)	20 (min)	30 (min)	45 (min)	60 (min)
AP3	27.99	42.25	54.24	60.26	83.62	90.26	97.21
AL6	26.98	40.64	51.26	59.56	80.42	88.21	94.89
AF9	26.21	39.98	50.16	59.11	79.42	87.42	94.21
AG12	18.21	27.21	36.46	45.64	49.06	55.56	62.26

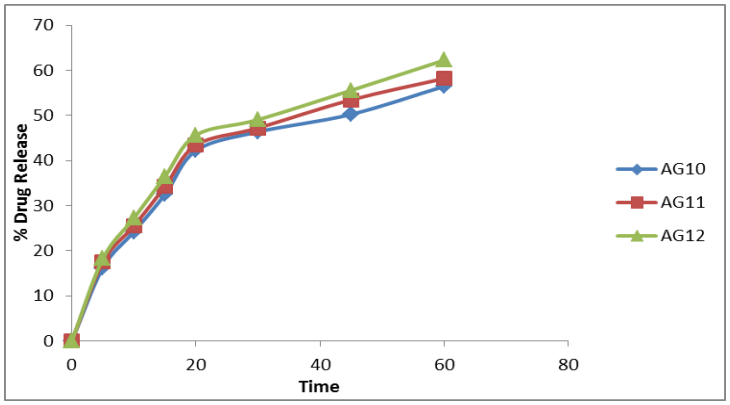

FIG. 5: COMPARISON OF DISSOLUTION PROFILE OF AG10, AG11, AG12 FORMULATION

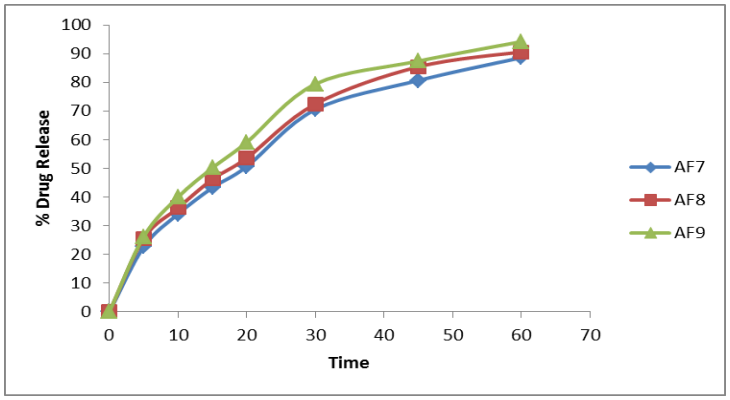

FIG. 6: COMPARISON OF DISSOLUTION PROFILE OF AF7, AF8, AF9 FORMULATION

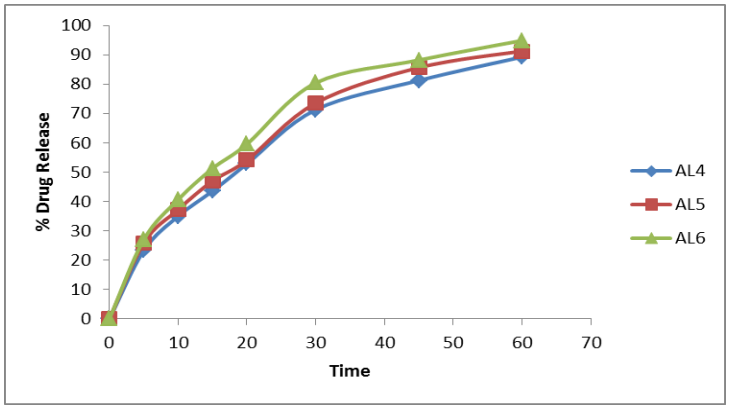

FIG. 7: COMPARISON OF DISSOLUTION PROFILE OF AL4, AL5 AND AL6 FORMULATION

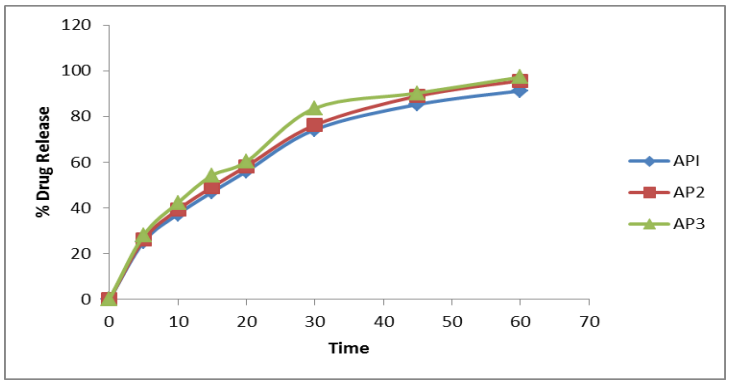

FIG. 8: COMPARISON OF DISSOLUTION PROFILE OF AP1, AP2 AND AP3 FORMULATION

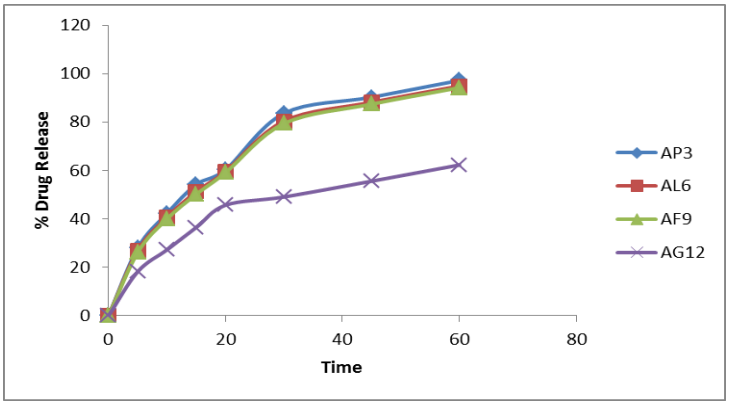

FIG. 9: COMPARISON OF DISSOLUTION PROFILE OF OPTIMIZED FORMULATIONS

CONCLUSION: From the present study, it can be concluded that natural superdisintegrant like mucilage of *Plantago ovata* showed better disintegration property and better in vitro dissolution profile than the other used natural superdisintegrant like Lepidium, Fenugreek and Guar gum in the formulations of FDTs.

ACKNOWLEDGEMENT: The author is thankful to Proffesor Vandana Arora, (Department of Pharmaceutics) Lloyd Institute of Management & Technology, Greater Noida (U.P), for providing the required facilities, guidance and support.

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How to cite this article:
Sharma V and Arora V: Comparison of various Natural Superdisintegrants in the Formulation of Fast Dissolving Carvedilol Tablet. *Int J Pharm Sci Res*. 3(10); 3947-3954.